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- (54) Anthelmintic paste compositions containing resins of  
**D,L-6-phenyl-2,3,5,6-tetrahydroimidazo(2,1-b)thiazole.**

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## Description

## SUMMARY OF THE INVENTION

5 The desirability of paste compositions for the oral administration of anthelmintic compositions is described in United States Patent No 3,746,490. The patent describes pastes of liquid dimethyl-2,2-dichlorovinyl phosphate (or DDVP) alone and contained in a polyvinyl chloride pellets.

Other anthelmintic paste compositions are described in United States Patent No 4,141,975, which describes an anthelmintic paste composition containing 0,0-dimethyl 1-hydroxy-2,2,2-trichloroethyl-phosphonate (Trichlorfon), and United States Patent No 4,277,467 which describes anthelmintic paste  
10 compositions containing trichlorfon and N-(2-methoxyacetamide-4-phenylthiophenyl)-N',N''-bis-methoxycarbonylguanidine (Febantel).

The use of 1-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole hydrochloride and trichlorfon, as a combination anthelmintic treatment, suitable for oral or parenteral administration is described in United States  
15 Patent No 3,937,825.

Previous attempts to prepare anthelmintic paste compositions containing two active ingredients such as the hydrochloride salt of dl-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole or l-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole, hereinafter referred to respectively as dl-tetramisole and l-tetramisole, with organophosphate anthelmintics such as trichlorfon, famphur, coumaphos, dimethoate, cythioate, chlorpyrifos  
20 and temephos, resulted in paste compositions which exhibit physical instability overtime and at elevated temperatures. These pastes shrink and separate upon aging and at elevated temperatures, giving compositions which are non-homogeneous and unsuitable for use.

It has been found that physically stable anthelmintic paste compositions containing dl-tetramisole and l-tetramisole in combination with the organophosphate compounds described above may be prepared when  
25 resinated dl- or l-tetramisole is used to prepare the anthelmintic combination pastes.

The present invention provides a physically stable anthelmintic paste composition comprising 2 % to 24 % on a weight basis of resinated l-tetramisole or resinated dl-tetramisole, 40 % to 75 % on a weight basis of heavy mineral oil, 0.0 % to 2.5 % on a weight basis of a nonionic surfactant, up to 31.0 % of an organophosphate compound as a second active ingredient 0 % to 5 % on a weight basis of an agent to  
30 increase the density of the composition such as barium sulfate, and 2 % to 10 % on a weight basis of a fumed or precipitated silica.

The resulting paste compositions exhibit greatly improved physical stability over extended periods of time and at elevated temperatures in comparison to paste compositions prepared using acid salts such as the hydrochloride salt of dl- or l-tetramisole.

35 Resinated forms of dl-tetramisole and l-tetramisole suitable for use in preparing paste compositions of the invention are described in United States Patent No 3,574,227. United States Patent No 3,574,227 addresses the problems associated with the bitter taste of these anthelmintics and their chemical instability which can result in chemical degradation and loss of potency when combined in animal feedstuffs. It has been found that resinated forms of dl-tetramisole and l-tetramisole may be used to prepare physically stable  
40 paste compositions containing other active ingredients such as the organophosphate compounds described above which are not compatible with the acid addition salts of dl-tetramisole and l-tetramisole.

Strongly acidic resins are preferred in the invention compositions since they provide resins in which the tetramisole is more strongly ionically bonded to the ion exchanged resin, thus substantially preventing ionization of the tetramisole. The preferred resins for the manufacture of the resins of the invention are  
45 the strongly acidic resins including sulfonated polystyrenes prepared from styrene and from about 1 to about 20 weight percent of divinyl benzene which functions as a cross-linking agent. Examples of resins useful in the invention include AMBERLITE® IR-120 and IR-112, and DOWEX® 50 and 50W resins; sulfonated phenolic resins including AMBERLITE® IR-1 resins; cellulose alkylsulfonic acid resins including Cellex SE resin; phenol methylene sulfonic acid resins including Acrolite C-131 resin; and sulfonated coal.

50 The reaction to form the tetramisole resins can be carried out within a wide temperature range so long as the solvent remains fluid and is not evaporated in excessive amounts. For example, temperatures of about -50°C to 150°C, and preferably between about 0°C and 100°C can be employed. Within the preferred temperature range, the reaction proceeds rapidly and loading of the resin is essentially complete. Generally 5 to 600,000 ppm, and preferably 100,000 to 300,000 ppm of the tetramisole compound are employed in  
55 the aqueous or organic solvent for use in the reaction.

The tetramisole solution can be contacted with the resin in any convenient manner such as passing the tetramisole solution through a resin bed or mixing the solution with finely divided resin particles. These particles are of a size between about 1700 to 38 µm (10 and 400 mesh) and preferably 1000 to 75 µm (16

to 200 mesh). The molar ratio of tetramisole to resin employed is not critical and is usually within the range of 0.125:1 to 3:1, preferably 0.5:1 to 2:1. A ratio falling within the preferred range permits most efficient loading of the resin within a reasonable period of time. There is little advantage to employing a reactant ratio outside the broad range since there is no significant improvement in either the amount or rate of ion exchange obtained. The tetramisole resins are suitable for use in accordance with this invention contain from about 1% to 56% by weight of tetramisole, and may be used directly in the preparation of pastes or may be milled to a particle size of 325 to 40  $\mu\text{m}$  (40-350 mesh) prior to use in preparing compositions of the invention.

The physically stable anthelmintic paste compositions of the invention may be prepared by admixing 40% to 75% on a weight basis of a heavy mineral oil with 0.0% to 2.5% on a weight basis of a nonionic surfactant such as Polysorbate 20, 2% to 24% on a weight basis of milled 325, 300, 150  $\mu\text{m}$  (40, 50, 100 mesh), I-tetramisole resinate up to 31% on a weight basis of an organophosphate compounds described above, 0% to 5% on a weight basis of an agent to increase the density of the composition such as barium sulfate, and 2% to 10% on a weight basis of a colloidal silica, until homogeneous mixture is obtained. The resulting mixture is then homogenized in a homogenizer such as Eppenbach Homomixer, yielding the desired physically stable viscous paste.

Anthelmintic paste compositions of the invention containing dl- or l-tetramisole as a resinate may include a wide variety of other active ingredients such as antibiotics, vaccines, vitamins, mineral supplements or mixtures thereof, preferably chlortetracycline, sulfamethazine, sulfethoxy pyridazine, sulfathiazole, tylosin or nitrofurantoin.

Throughout the text, the organophosphate compounds are referred to by generic names. A complete listing of the corresponding chemical names is given below.

Trichlorfon	O,O-dimethyl l-hydroxy-2,2,2-trichloroethylphosphonate
Famphur	O,O-dimethyl O-p-(dimethylsulfamoyl)phenyl phosphorothioate
Coumaphos	O-(3-chloro-4-methyl-2-oxo-2H-benzopyran-7-yl) O,O-diethyl phosphorothioate
Dimethoate	O,O-dimethyl S-[2-(methylamino)-2-oxo-ethyl] phosphorodithioate
Cythioate	phenyl O,O-dimethyl O-p-sulfamoyl phosphorothioate
Chlorpyrifos	O,O-diethyl O-(3,5,6-trichloro-2-pyridyl)phosphorothioate
Temephos	O,O'-(thiodi-4,1-phenylene)bis(O,O-dimethyl phosphorothioate)

#### EXAMPLE 1

Polysorbate 20 60 g, 1.50% on a weight basis is added to heavy mineral oil 2164.64 g, 53.12% on a weight basis and the resulting mixture agitated in a Ross double planetary mixer for five minutes. I-Tetramisole resinate 460 g, 11.50 on a weight basis is then added, after mixing for five minutes, a preblend, 1226 g, 30.65% on a weight basis, comprised of mixture of technical trichlorfon (96.2% pure) 97.5% by weight and fumed silica, 2.5% by weight which has been milled to a mean particle size of 62  $\mu\text{m}$  is added. After blending for ten minutes fumed silica 3.23% on a weight basis is added and blending continued for 15 minutes. The resulting mixture is homogenized in a Homomixer, yielding the desired anthelmintic paste combination composition.

By utilizing the above procedure and substituting the appropriate components, the paste compositions summarized in Table I below may be prepared.

TABLE I

Composition of Component	1	2	3	4	5	6	7	8	9	10
	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
1-tetramisole HCl	5.83 (5.75)	5.83 (5.75)	12.28 (11.72)	-	-	-	-	-	-	-
Resinate	-	-	-	12.00* (5.75)	12.0 (5.75)	12.0 (5.75)	12.0 (5.75)	11.50 (5.75)	11.50 (5.75)	11.50 (5.75)
Famphur	29.06	-	-	-	29.2* (28.47)	29.2* (28.47)	29.2* (28.47)	-	-	-
Trichlorfon	-	29.06	-	30.00* (28.75)	-	-	-	30.65* (40.0)	30.81* (30.0)	30.81* (30.0)
Polysorbate 20	1.0	1.0	1.01	1.50	0.7	1.10	1.50	1.50	1.50	1.50
Colloidal silica	2.75	2.75	3.55	2.90	3.00	2.75	2.75	3.23	3.23	3.23
BaSO <sub>4</sub>	5.00	5.00	10.15	5.00	5.00	5.00	5.00	-	-	-
Heavy mineral oil	56.36	56.36	72.99	48.6	50.1	49.95	49.55	53.116	52.96	52.96

\*Premix containing 1% to 3% by weight of fumed silica from milling.

( ) Denotes % active ingredient, figuring for 1-tetramisole expressed as HCl equivalent.

## EXAMPLE 2

Physical stability of anthelmintic paste compositions

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The physical stability of the anthelmintic paste compositions of the invention is evaluated by storing samples at 37°C and 45°C and visually inspecting the paste periodically for shrinkage or clear liquid formation.

The results of these experiments summarized in Table II below demonstrate the enhanced physical stability of anthelmintic paste compositions containing resinated l-tetramisole and organophosphate compounds compared to the control combinations which are prepared using the hydrochloride salt.

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TABLE II  
Stability of paste compositions

Composition of	1	2	3	4	5	6	7	8	9	10
Stability	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
37°C										
2 months	Separates	Separates								
3 months								Stable	Stable	Stable
6 months					Stable	Stable	Stable			
45°C										
1 months	Separates	Separates								
2 months			Stable							
6 months				Stable	Stable	Stable	Stable			

## Claims

1. A physically stable anthelmintic paste composition comprising 2 % to 24 % on a weight basis of resinated l-tetramisole or resinated dl-tetramisole, 40 % to 75 % on a weight basis of heavy mineral oil,

0.0 % to 2.5 % on a weight basis of a nonionic surfactant, up to 31.0 % of an organophosphate compound as a second active ingredient, 0 % to 5 % on a weight basis of an agent to increase the density of the composition such as barium sulfate, and 2 % to 10 % on a weight basis of a fumed or precipitated silica.

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2. A composition according to Claim 1, wherein the second active ingredient is an organophosphate compound selected from famphur, trichlorfon, coumaphos, dimethoate, cythioate, chlorpyrifos, or temephos.

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3. A composition according to Claim 2, wherein the second active ingredient is trichlorfon.

4. A composition according to Claim 2, wherein the second active ingredient is famphur.

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5. A composition according to Claim 1, further comprising up to 31.0 % of an antibiotic such as chlortetracycline, sulfamethazine, sulfethoxypyridazine, sulfathiazole, tylosin or nitrofurantoin.

6. A composition according to Claim 1, further comprising up to 31.0 % of a vaccine.

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7. A composition according to Claim 1, further comprising up to 31.0 % of a vitamin, a mineral supplement or a mixture thereof.

#### Patentansprüche

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1. Physikalisch stabile anthelmintische Pastenzubereitung umfassend, in Gew.-%, 2 bis 24% des Resinats von l-Tetramisol oder von dl-Tetramisol, 40 bis 75% schweres Mineralöl, 0,0 bis 2,5% eines nichtionischen oberflächenaktiven Mittels, bis zu 31,0% einer Organophosphatverbindung als zweitem aktiven Bestandteil, 0 bis 5% eines Mittels zur Erhöhung der Dichte der Zubereitung, wie Bariumsulfat, und 2 bis 10% eines pyrogenen oder gefüllten Siliziumdioxids.

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2. Zubereitung nach Anspruch 1, worin der zweite aktive Bestandteil eine Organophosphatverbindung ist, ausgewählt aus Famphur, Trichlorfon, Coumaphos, Dimethoat, Cythioat, Chlorpyrifos oder Temephos.

3. Zubereitung nach Anspruch 2, worin der zweite aktive Bestandteil Trichlorfon ist.

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4. Zubereitung nach Anspruch 2, worin der zweite aktive Bestandteil Famphur ist.

5. Zubereitung nach Anspruch 1, weiter umfassend bis zu 31% eines Antibiotikums, wie Chlortetracyclin, Sulfamethazin, Sulfethoxypyridazin, Sulfathiazol, Tylosin oder Nitrofurantoin.

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6. Zubereitung nach Anspruch 1, weiter umfassend bis zu 31% eines Vaccins.

7. Zubereitung nach Anspruch 1, weiter umfassend bis zu 31% eines Vitamins, eines Mineralzusatzes oder einer Mischung davon.

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#### Revendications

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1. Composition de pâte anthelmintique physiquement stable comprenant 2% à 24%, sur une base pondérale, de l-tétramisole en résine ou de dl-tétramisole en résine, 40% à 75%, sur une base pondérale, d'huile minérale lourde, 0,0% à 2,5%, sur une base pondérale, d'un tensioactif non ionique, jusqu'à 31,0% d'un composé organophosphate comme second ingrédient actif, 0% à 5%, sur une base pondérale, d'un agent servant à augmenter la densité de la composition, comme le sulfate de baryum, et 2% à 10%, sur une base pondérale, d'une silice fumée ou précipitée.

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2. Composition selon la revendication 1, dans laquelle le second ingrédient actif est un composé organophosphate choisi parmi le famphur, le trichlorfon, le coumaphos, le diméthoate, le cythioate, le chlorpyrifos ou le téméphos.

3. Composition selon la revendication 2, dans laquelle le second ingrédient actif est le trichlorfon.

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4. Composition selon la revendication 2, dans laquelle le second ingrédient actif est le famphur.
- 5 5. Composition selon la revendication 1, comprenant, en outre, jusqu'à 31,0% d'un antibiotique tel que la chlortétracycline, la sulfaméthazine, la sulféthoxypyridazine, le sulfathioazole, la tylosine ou le nitrofuranne.
6. Composition selon la revendication 1, comprenant, en outre, jusqu'à 31,0% d'un vaccin.
- 10 7. Composition selon la revendication 1, comprenant, en outre, jusqu'à 31,0% d'une vitamine, d'un supplément minéral ou d'un de leurs mélanges.

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